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EFFICACY OF BOTULINUM TOXIN TYPE B (MYOBLOC™) FOR TREATMENT OF BLEPHAROSPASM: REPORT OF TWO CASES

M. Stacy[1] and J. Samanta[1]

Blepharospasm is a focal dystonia that causes involuntary closure of the eyelids. Botulinum toxin is the treatment of choice. Botulinum toxin type B (MYOBLOC™) is approved by the U.S. Food and Drug Administration for treatment of cervical dystonia, but has not been approved for blepharospasm. Patient SL is a 67-year-old woman who had received botulinum toxin type A (Botox) since 1997, but experienced decreasing magnitude and duration of benefit despite an increase of dose from 36 U to 52 U. She was treated with 2600 U Myobloc injected into 10 sites. Treatment resulted in reduced involuntary movements. On follow-up, she was reinjected with 3600 U Myobloc. Patient CG is a 46-year-old woman who had been treated with Botox since 1999 with decreasing benefit despite a dose increase from 55 U to 80 U. Her last injection brought her very little relief, with involuntary movements rated 3 on a 4-point scale. She received 4000 U Myobloc spread over 10 sites. Onset of benefit was within 2 days, and duration of benefit was 7 weeks. During this time, she rated her involuntary movements as 0.5, a marked improvement from baseline and her previous treatment. She was reinjected with 4400 U Myobloc. Neither patient reported adverse effects from treatment. Follow-up is ongoing for both patients, and updated results will be presented. We conclude Myobloc may be an effective treatment for blepharospasm.

[1]Muhammad Ali Parkinson Research Center, Phoenix, AZ 85013 USA

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THE USE OF BOTULINUM TOXIN FOR INTERNAL ROTATION CONTRACTURE OF THE SHOULDER IN OBSTETRIC BRACHIAL PLEXUS PALSY

JS Stanton, L C Bainbridge

In obstetric brachial plexus palsy an internal rotation contracture of the shoulder occurs due to the unopposed action of subscapularis. This is treated by subscapularis tendon lengthening with or without a coracoid excision. We present the first experience with the use of botulinum toxin to selectively defunction the subscapularis and allow improved function

There were 12 patients in this series with an average age of 41 months, in 10 cases the right shoulder being affected. Four patients were Gilbert & Tassin Grade 1 and 8 patients were Grade 2. All of the patients were noted to have very restricted external rotation with consequent marked shoulder deformity. The injections were carried out under general anaesthesia using stimulating needles placed deep to the vertical border of the scapula. Eight of the patients also had coracoidectomy. None of the patients had postoperative splintage. Physiotherapy was carried out locally and they were assessed at 2 weeks, 6 weeks and 3 months.

The average passive external rotation of the shoulder increased by 40° and subjective assessment by the parents of overall shoulder function was very encouraging.

Botulinum toxin inactivation of subscapularis followed by physiotherapy is a simple procedure preventing the need for operation in those not requiring coracoidectomy. As with all procedures around the shoulder it is preferable to carry out treatment earlier to prevent bony deformity.

Pulvertaft Hand Centre, Derbyshire Royal Infirmary, London Road, Derby, UK

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NEUROTOXINS IN STUDIES OF CELL MEMBRANE REPAIR AND CHANNEL ACTIVATION

R.A. Steinhardt, T. Togo, and J.M. Alderton

Neuotoxins have played a critical role in uncovering exocytotic-dependent mechanisms in cell biology. Disruption of plasma membranes evokes a Ca^{2+}- regulated exocytosis near the wound site, which is required for membrane resealing. The use of neurotoxins first uncovered the requirement for SNARES and exocytosis in cell membrane repair. Exocytosis is needed to lower membrane tension to the point where the bilayer can reseal. Artificial lowering of tension can obviate the requirement for exocytosis. Studies of the exocytotic-dependent cell membrane repair have led to the discovery that repeated membrane disruptions evoke a long-term potentiation of Ca^{2+}-regulated exocytosis which is closely correlated with faster membrane resealing rates. This potentiation of exocytosis is cAMP-dependent protein kinase (PKA)-dependent in the early stages (minutes), in the intermediate-term (hours) requires protein synthesis, and for long-term (24 hours) depends on the activation of cAMP responsive element-binding protein (CREB). The use of neurotoxins has also demonstrated that the inhibition of exocytosis can block store-operated calcium entry and supports a model in which vesicle fusion is a prerequisite for activation of store-operated calcium channels.

Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720-3200, USA

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BONT/A LIGHT CHAIN AND THE DILEUCINE MOTIF: POTENTIAL IMPLICATIONS FOR LIGHT CHAIN LOCALIZATION AND NEUROTOXIN DURATION OF ACTION

L.E. Steward, E. Fernandoz-Salas, H. Ho, S.W. Sun, J.V. Ordas, L. Zhang, T.M. Herrington, K. R. Aoki

The neuroparalytic effect of the botulinum neurotoxins has been effectively exploited for the treatment of several neuromuscular diseases. It is well established that the duration of botulinum neurotoxin induced neuroparalysis is substantially varied for differing serotypes. In humans, BoNT/A has the longest duration of action and BoNT/E has the shortest duration of action. Recently it has been demonstrated that BoNT/A, /B, and /E light chains are differentially localized when expressed in PC12 cells (reported in a separate abstract). Differential localization of LC's is an intriguing characteristic of the BoNTs and has led us to hypothesize that localization of LCs within neurons, or the lack thereof, may play a role in the toxin duration of action.

The sequences of LC/A, LC/B, and LC/E were analyzed for the presence of localization signals. A putative dileucine motif was identified at the C-terminus of LC/A and was unique to that serotype. The role of the dileucine motif in LC/A activity as well as localization was investigated. We observed that a LC/A construct that lacks 9 N-terminal and 22 C-terminal amino acids (including the dileucine motif) retains minimal activity and is mislocalized when expressed in PC12 cells. The specific role of the dileucine motif was investigated by generating a LL→AA double mutant. The LL→AA mutant has minimally reduced activity, but is mislocalized when expressed in PC12 cells. The mislocalization is similar to that recently reported for the LL→AA mutant of VAMP4. Localization and activity data are reported, supporting the hypothesis that the dileucine motif is important for proper intracellular localization of LC/A.

Allergan, Inc.; P.O. Box 19534, Irvine, CA 92623-9534; USA